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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
DELACROIX MUIRHEI, CYBILLE	
ART UNIT	PAPER NUMBER
1614	

DATE MAILED: 08/03/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/768,445	HOUGHTON, PETER J.	
	Examiner	Art Unit	
	Cybille Delacroix-Muirheid	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 October 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2 and 4-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2 and 4-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/06/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Detailed Action

1. Claims 1-2, 4-25 are rejected under 35 U.S.C. 1 12, first paragraph, because the specification, while being enabling the treatment of neuroblastoma, glioblastoma and rhabdomyosarcoma, does not reasonably provide enablement for the treatment of all types of cancer using the claimed compounds. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

2. Claims 1-2, 4-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Burton et al. and Ragab 6,346,524 (submitted by Applicant) in view of Friedman 6,251,886.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Response to Amendment(s)

The following is responsive to applicant's amendment received Oct. 6, 2005.

Claims 3 and 26 are cancelled. No new claims are added. Claims 1-2, 4-25 are currently pending.

The previous rejection of claim 26 under 35 USC 103(a) over Burton et al. and Ragab 6,346,524 in view of Friedman, 6,251,886, set forth in paragraph 3 of the office action mailed April 7, 2005 is withdrawn in view of applicant's amendment canceling claim 26.

However, applicant's arguments traversing (1) the previous claim rejection under 35 USC 112, first paragraph (scope of enablement, see paragraph 1 above) and (2) the previous claim rejection under 35 USC 103(a) over Burton et al. and Ragab in view of Friedman (see paragraph 2 above) have been carefully considered but are not found to be persuasive.

Said rejections are maintained for reasons given previously in the office actions mailed April 7, 2005 and June 17, 2004 with the following additional comment.

Claim Rejection(s)—35 USC 112, first paragraph (scope of enablement): Applicant's arguments are as follows.

Applicant respectfully states that per the Wands factors, that applicant has enabled the claims to treat cancer. With regard to the state of prior art, applicant respectfully points out as per the first page of applicant's specification and the Examiner's own references, that the claimed compounds have an effect on a number of cancers. Burton shows the anti-tumor effect on tumor DNA of irinotecan (see Burton, page 3, middle two paragraphs). Applicant additionally suggests that cancers, other than those specified by the Examiner, can be treated by these compounds due to general cytotoxic chemotherapeutic action they inflict on tumor DNA. Therefore, these compounds are enabled by the art and the specification to treat cancer. In support of this, applicants refer the Examiner to the references cited on page 1 of the specification. Applicant suggests that the examples provided in the specification on pages 7-24, in addition to the general knowledge in the art, provide ample support to alleviate the burden of undue experimentation to one of ordinary skill in the art.

Said arguments have been considered but are not found to be persuasive.

The present specification is evaluated by the Examiner as directed by the Court in *In re Marzocchi et al.*, 169 USPQ 367 (CCPA 1971):

"Specification disclosure which contains teaching of manner and process of making and using the invention in terms corresponding to the scope to those used in describing and defining subject matter sought to be patented must be taken as in compliance with enabling requirement of first paragraph of 35 U.S.C. 112 *unless there is reason to doubt the objective truth of statements contain therein which must be relied on for enabling support*; assuming that sufficient reason for such doubt exists, a rejection for failure to teach how to make and/or use will be

proper on that basis, such a rejection can be overcome by suitable proofs indicating that teaching contained in specification is truly enabling." (emphasis added).

Here, the objective truth that all cancers, known to one of ordinary skill in the art can be "synergistically" treated (see applicant's remarks page 9 of the amendment of Oct. 6, 2005) by administration of temozolomide in combination with irinotecan is doubted. The state of the art with regard to treating cancer broadly is underdeveloped and highly unpredictable (please refer to item (2) of the scope of enablement rejection in the office action mailed June 17, 2004). In particular, there is no known anticancer agent or combination of agents effective against all cancer types. The Goodman & Gilman reference (cited by Examiner) clearly shows that for the various known cancer types, there is not one specific chemotherapeutic agent or combination of agents that is effective for each and every type of cancer. Moreover, the references referred to at page 1 of the specification do not recognize the ability of temozolomide or irinotecan to treat all kinds of cancer. The cited journal articles on page 1 of the specification discuss temozolomide's activity against melanoma. Therefore, the examiner is compelled to doubt that all cancers can be treated by the claimed combination.

According to MPEP 2164.08, the Federal Circuit has repeatedly held that "the specification must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation'." In re Wright, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). All that is necessary is that one skilled in the art be able to practice the claimed invention, given the level of knowledge and skill in the art. Further the scope of enablement must only bear a "reasonable correlation" to the scope of the claims. See, e.g., In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

As concerns the breadth of a claim relevant to enablement, the only relevant concern should be whether the scope of enablement provided to one skilled in the art by the disclosure is commensurate with the scope of protection sought by the claims. > AK Steel Corp. v. Sollac, 344 F.3d 1234, 1244, 68 USPQ2d 1280, 1287 (Fed. Cir. 2003);< In re Moore, 439 F.2d 1232, 1236, 169 USPQ 236, 239 (CCPA 1971). See also Plant Genetic Sys., N.V. v. DeKalb Genetics Corp., 315 F.3d 1335, 1339, 65 USPQ2d 1452, 1455 (Fed. Cir. 2003).

In this case, the Examiner respectfully submits that the scope of enablement in the disclosure does not bear a "reasonable correlation" to the scope of the claims. It is acknowledged that Applicant is not required to enable each and every single embodiment encompassed by the claims, but must enable a sufficient number to be reasonably representative of that which is claimed. However, applicant has not provided any evidence or persuasive argument in the present disclosure or in the response to the rejection made under 35 USC 112, first paragraph, as to how the examples and data shown in the specification are reasonably representative of the treatment of cancer ***in general***. In the absence of any sound evidence or scientific reasoning as to how the skilled artisan would extrapolate any results from studies involving only neuroblastoma, glioblastoma and rhabdomyosarcoma in the present disclosure as being reasonably suggestive of treating cancer (in general), the present disclosure is not determined to be enabling for the treatment of all types of cancers.

Additionally, in light of the state of the art, which conspicuously lacks recognition that all forms of cancer are treatable by the administration of one drug or one combination of drugs, and in view of the unpredictability of effectively treating cancer, it is highly unlikely, and the Office would require experimental evidence to support the contention, that the claimed combination

could actually treat, especially in a synergistic manner (as argued by applicant on page 9 of the response), all cancers by simply administering, by any method, an amount of the claimed active agents.

Given what is presently claimed, what is presently disclosed, and given what is supported by adequate description in the specification, one of ordinary skill in the art would have no alternative recourse ***but*** undue experimentation in order to determine how the present invention could be used to treat all forms of cancer.

It is for these reasons that the rejection stands.

Claim Rejection(s)—35 USC 103(a) over Burton et al. and Ragab 6,346,524 in view of Friedman 6,251,886: Applicant's arguments are as follows.

Applicant argues that the examiner has not established a prima facie case of obviousness. Applicant claims a method of treatment using therapeutically effective amounts of temozolomide in *combination* with irinotecan. Therapeutically effective amounts temozolomide and irinotecan are described on pages 4-6 of the specification. On the other hand, Ragab and Burton et al. do not teach or suggest a method of treating certain cancers by administering a combination of irinotecan and temozolomide to a patient suffering from the cancer. In fact, applicant submits that Burton et al. teach away from the claimed invention by the fact that it mentions both monotherapy with irinotecan and temozolomide. Neither Ragab nor Burton et al. disclose combining irinotecan and temozolomide as claimed by applicant.

Regarding Friedman, applicant contends that Friedman is silent with respect to administering irinotecan and temozolomide over repeated 21 day cycles, where the 21 day cycles are divided into three 1 week periods.

Finally, the efficacy of a drug with respect to a particular disease cannot be predicted based upon treatment of that disease with a structurally and functionally distinct drug, such as irinotecan and temozolomide. The references cited by the Examiner are not predictive of treating cancer with irinotecan and temozolomide, with the 21 day cycles, especially due to the *synergistic* effects demonstrated in the specification by Example C, starting on page 7, line 20 to page 10, line 23. Therefore, applicant respectfully submits that the claimed invention is not obvious in light of Friedman, Ragab and Burton et al.

Said arguments have been considered but are not found to be persuasive.

The examiner recognizes that there is no express motivation in the prior art to combine the two chemotherapeutic agents for the treatment of some cancers. However, it would have been obvious to one of ordinary skill in the art at the time the invention was made to further modify the methods of the prior art by combining temozolomide with irinotecan because one of ordinary skill in the art would reasonably expect these chemotherapeutic compounds to be more effective in combination resulting in at least an additive effect against certain cancer cells such as gliomas. Additionally, Burton, Ragab and Friedman teach that temozolomide and irinotecan are known in the art to be useful for treating certain cancers such as gliomas. Absent evidence to the contrary, modification to combine these agents both of which are known to be useful for the same purpose, would have been obvious to one of ordinary skill in the art in view of the fact that the courts have held "it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition which is to be used for the very same purpose". Please see In re Susi, 169 USPQ 423, 426 (CCPA 1971); In re Kerkhoven, 205 USPQ 1069 (CCPA 1980).

Regarding applicant's argument that the prior art, especially Friedman, does not disclose administering irinotecan and temozolomide over repeated 21 day cycles, where the 21 day cycles are divided into three 1 week periods, the examiner respectfully submits that this would have been obvious in view of the prior art. The court has held "it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 105 USPQ 233, 235 (CCPA 1955). Only if "the results of optimizing a variable are 'unexpectedly good' can a patent be obtained for a claimed critical range." In re Antonie, 195 USPQ 6, 8 (CCPA 1977). See also In re Geisler, 43 USPQ2d 1362 (CAFC 1997). Therefore, the Examiner respectfully submits, in view of Ragab, Burton and Friedman, and absent evidence of unexpected results, it would have been prima facie obviousness to arrive at the claimed dosing schedule. The Examiner respectfully maintains since Ragab, as well as Burton et al., have established that the therapeutic efficacy of temozolomide and irinotecan is dependent upon treatment cycles and dosing schedules (see again page 7-8 of the office action mailed April 7, 2005), it would have been obvious to one of ordinary skill in the art at the time the invention was made to further modify the methods the prior art such that temozolomide and irinotecan are administered according to a schedule that is effective to inhibit the cancer being treated.

With respect to applicant's remarks regarding the predictability of drug efficacy, the Federal Circuit has held "all that is required for obviousness under §103 is a reasonable expectation of success." Please see In re O'Farrell, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988). Additionally, "obviousness does not require absolute predictability." In re Ball Corp., 10 USPQ 2d 1491 (Fed. Cir. 1991). Ragab, Burton and Friedman may not specifically disclose treating certain cancer cells with a combination of temozolomide and irinotecan. However, Friedman

teaches, and therefore suggests, that temozolomide may be administered in combination with another chemotherapeutic agent such as irinotecan (please see col. 13, lines 1-5). Based on this teaching, one of ordinary skill in the art would reasonably expect temozolomide in combination with irinotecan to demonstrate effective inhibition of the cancer cells.

Finally, applicant offers evidence of synergy in the claimed method by referring the examiner to the specification, Example C, page 7, line 20 to page 10, line 23. The examiner has reviewed the information provided in Example C. Synergism against neuroblastoma, rhabdomyosarcoma and glioblastoma is observed for the administration of temozolomide and irinotecan as claimed. However, applicant is reminded "objective evidence of nonobviousness must be commensurate in scope with the claims which the evidence is offered to support." In other words, the showing of unexpected results must be reviewed to see if the results occur over the entire claimed range. In re Clemens, 622 F.2d 1029, 1036, 206 USPQ 289, 296 (CCPA 1980). In this case, the examiner respectfully submits that applicant's arguments and objective evidence are not commensurate in scope with the claimed methods. Experiments limited to inhibition of three types of cancer using the claimed active agents and treatment cycle are not commensurate in scope with the claims. There is no adequate basis for reasonably concluding that the great number and variety of cancers included in the claims would be inhibited in the same synergistic manner as the neuroblastoma, rhabdomyosarcoma and glioblastoma cells. Please also see MPEP 716.02(d) and In re Lindner, 457 F.2d 506, 509, 173 USPQ 356, 359 (CCPA 1972) (Evidence of nonobviousness consisted of comparing a single composition within the broad scope of the claims with the prior art. The court did not find the evidence sufficient to rebut the prima facie case of obviousness because there was "no adequate basis for reasonably

concluding that the great number and variety of compositions included in the claims would behave in the same manner as the tested composition."). Additionally, synergism against the specific cancers is only observed using the dosage amounts discussed in Example C. Such dosage amounts are also not commensurate in scope with the claimed method.

It is for these reasons that the rejection is maintained.

Conclusion

Claims 1-2, 4-25 stand rejected.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Cybille Delacroix-Muirheid** whose telephone number is **571-272-0572**. The examiner can normally be reached on Mon-Thurs. from 8:30 to 6:00 as well as every other Friday from 9:30-6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Ardin Marschel**, can be reached on **571-272-0718**. The fax phone number for the organization where this application or proceeding is assigned is **571-273-8300**.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

CDM
August 1, 2006

Ardin H. Marschel 8/1/06
ARDIN H. MARSCHEL
SUPERVISORY PATENT EXAMINER